

Role of specific IgE and skin-prick testing in predicting food challenge results to baked egg

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ABSTRACT

Previous studies suggest that children with egg allergy may be able to tolerate baked egg. Reliable predictors of a successful baked egg challenge are not well established. We examined egg white-specific IgE levels, skin-prick test (SPT) results, and age as predictors of baked egg oral food challenge (OFC) outcomes. We conducted a retrospective chart review of children, aged 2–18 years, receiving an egg white-specific IgE level, SPT, and OFC to baked egg from 2008 to 2010. Fifty-two oral baked egg challenges were conducted. Of the 52 challenges, 83% (n = 43) passed and 17% (n = 9) failed, including 2 having anaphylaxis. Median SPT wheal size was 12 mm (range, 0–35 mm) for passed challenges and 17 mm (range, 10–30 mm) for failed challenges (p = 0.091). The negative predictive value for passing the OFC was 100% (9 of 9) if SPT wheal size was <10 mm. Median egg white-specific IgE was 2.02 kU/L (range, <0.35–13.00 kU/L) for passed challenges and 1.52 kU/L (range, 0.51–6.10 kU/L) for failed challenges (p = 0.660). Receiver operating characteristic (ROC) curve analysis for SPT revealed an area under the curve (AUC) of 0.64. ROC curve analysis for egg white-specific IgE revealed an AUC of 0.63. There was no significant difference in age between patients who failed and those who passed (median = 8.8 years versus 7.0 years; p = 0.721). Based on our sample, SPT, egg white-specific IgE and age are not good predictors of passing a baked egg challenge. However, there was a trend for more predictability with SPT wheal size.

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Egg allergy is one of the most common food allergies in infants and young children with an estimated prevalence between 0.5 and 2.5%.¹ A standard diagnostic approach includes a thorough clinical history in combination with skin-prick testing (SPT) and food-specific IgE values to egg white. Treatment recommendations have included strict avoidance of egg, including baked products containing egg, with the theory that even minute ingestions could provoke symptoms or even delay natural resolution of the egg allergy. Another theory suggests that the early introduction of foods may induce tolerance. It has recently been reported that many children with egg allergy may actually be able to tolerate heated or baked egg.^{2–5} The mechanism for heated egg tolerance is related to egg

proteins being denatured during the heating process, thereby, diminishing the allergenicity. Predictors of tolerance to baked egg may improve quality of life in food-allergic children because baked egg is found in so many foods.

Retrospective and prospective studies have now reported that 55–93% of children with egg allergy are able to tolerate baked egg without reaction.^{2–5} Furthermore, recent studies suggest that regular consumption of baked egg products may actually hasten the natural resolution of egg allergy⁴ and even show a reduction in egg SPT size after heated egg is introduced into an egg-allergic individual's diet.⁵ However, given that some egg-allergic individuals do not tolerate baked egg, establishing predictors for baked egg oral food challenge (OFC) outcomes will be clinically useful in identifying egg-allergic individuals who may tolerate baked egg. Physician-supervised OFCs remain the gold standard for food allergy diagnosis.^{6,7} In this study, we examined SPT results, food-specific IgE values, and age as predictors of baked egg OFC outcomes.

METHODS

We retrospectively analyzed the clinical history of all subjects with documented IgE-mediated egg allergy who underwent an OFC to baked egg from April 2008 to October 2010 at Children's Hospital Boston. The decision to perform the OFC was made by allergy

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Allergy/Immunology Program

BAKED EGG CHALLENGE - INSTRUCTIONS FOR PARENTS

Muffin/Cupcake preparation

Muffins/Cupcakes will need to be prepared at home and brought to the visit. **Please bring 2 large muffins/cupcakes (made in a 6 muffin/cupcake pan) or 4 small muffins/cupcakes (made in a 12 muffin/cupcake pan). Please be sure to use 2 large eggs in recipe.**

Please follow the directions below in order to ensure that your child gets enough egg protein to complete the challenge successfully. The muffin/cupcake mix may contain other ingredients that are allergic foods for your child. If your child has other food allergies, please use substitutions appropriate for your child.

Muffin/Cupcake Mix Containing Baked Egg

1. **You may use a muffin mix or other cake type recipe that requires 2 large eggs.**
Follow recipe according to package directions.
2. **Please be sure to use 2 large eggs in recipe.**
3. Use a standard 6 muffin/cupcake pan (for 6 large muffins/cupcakes) or a 12 muffin/cupcake pan (for 12 small muffins/cupcakes). Coat each muffin cup lightly with vegetable oil spray or use a paper muffin cup.
4. Distribute the batter EQUALLY among the cups. Bake 30 MINUTES or more at 375°F.

Figure 1. Baked egg recipe for parents.

providers from our single center practice at Children's Hospital Boston. In addition to evaluating the OFC outcomes, we analyzed the patient demographics, clinical allergy history, most recent food-specific IgE testing (egg white and, if available, ovomucoid), and most recent SPT results to egg white before the OFC. Ovomucoid-specific IgE was evaluated because it is heat resistant, remains soluble after extensive heating, and is the dominant allergen in hen's egg white.⁸ The study was approved by the Institutional Review Board of Children's Hospital Boston.

OFC Procedure

OFCs were performed as graded open challenges according to recommendations of the American Academy of Asthma, Allergy, and Immunology and the American College of Allergy, Asthma, and Immunology.⁹ The challenge food consisted of muffins or cupcakes baked by the parents according to a standard recipe we provided as seen in Fig. 1. The recipe included two large eggs, including both egg whites and yolks. The challenge food was slowly given in increasing amounts to a total dose of baked product containing approximately one-third of an egg (~2.2 g of egg protein). Subjects were monitored for 1 hour after the challenge or longer if they failed the challenge.

SPT and Food-Specific IgE Testing Procedures

All subjects avoided short-acting antihistamines for 3 days and long-acting antihistamines for 10 days before

SPT. Skin testing was performed by technicians trained in our clinic to use the same technique. The SPT was performed in a standard fashion using the Multi-Test II device from Alk-Abello (Round Rock, TX) and a commercially prepared, standardized egg white extract from Greer Laboratories (Lenoir, NC). Negative controls with saline and positive controls with histamine were performed concurrently. The longest diameter was measured in millimeters at 15 minutes. A positive SPT was defined as a wheal diameter ≥ 3 mm larger than the negative control.

Food-specific IgE levels for egg white and ovomucoid were measured using an ImmunoCAP fluorescence enzyme immunoassay (Phadia AB, Uppsala, Sweden). The lower limit of detection (LLOD) for egg white-specific IgE was 0.35 kU/L and for ovomucoid-specific IgE was 0.10 kU/L. For any calculations, we used values of 0.35 and 0.10 kU/L when the reported laboratory result was less than the LLOD. For analysis, we evaluated the most recent SPT and food-specific IgE testing before the food challenge. With the exception of one subject (who passed the challenge), each subject had either an egg white-specific IgE level or egg white SPT obtained within a year of the OFC and, in some cases, both were obtained within a year.

Statistical Analysis

For statistical evaluation, median values were calculated for sets of SPT wheal sizes and food-specific IgE levels. The *p* values were determined by using the

Table 1 Baseline characteristics

	Frequency (<i>n</i> = 52)
Age at testing	
2–5 yr	33% (17)
6–8 yr	42% (22)
≥9 yr	25% (13)
Gender	
Male	56% (29)
Female	44% (23)
History of egg anaphylaxis	
Yes	6% (3)
No	94% (49)
History of other food allergies	
Yes	98% (51)
No	2% (1)
History of other atopic conditions (atopic dermatitis, allergic rhinitis, and asthma)	
Yes	94% (49)
No	6% (3)
Recent objective evaluation for egg allergy	
Egg white SPT and egg white-specific IgE	73% (38)
Egg white SPT only	13% (7)
Egg white-specific IgE only	13% (7)
Egg white SPT and/or egg white-specific IgE	100% (52)
<i>SPT</i> = skin-prick test.	

Mann-Whitney *U* test for comparison of independent samples.

Receiver operating characteristic (ROC) curve analysis was used to determine a threshold that would differentiate children who would react to baked egg from those who are tolerant. The relationship between sensitization status and outcome measure was analyzed using logistic regression. In addition, fitted predicted probability curves were created from the logistic regression models.

RESULTS

Fifty-two egg-allergic children (56% boys) with a median age of 7.2 years (range, 2.2–18.0 years) underwent a baked egg challenge. Baseline characteristics of the subjects are shown in Table 1. At the time of OFC, most patients had other atopic conditions such as other food allergies, asthma, atopic dermatitis, and allergic rhinitis. Three subjects (6%) had a history of egg anaphylaxis. Before baked egg challenges, all subjects had at least one of the following tests: (1) SPT to egg white or (2) blood test for egg white-specific IgE. The major-

ity (73% or 38 subjects) had both an SPT and an egg white-specific IgE blood test performed before the OFC. The median egg SPT wheal size was 13 mm (range, 0–35 mm). The median egg white-specific IgE was 1.99 kU/L (range, <0.35–13.00 kU/L). Four values were below the LLOD.

Forty-three subjects (83%) passed and nine subjects (17%) failed the OFC. The characteristics of the children who failed the challenge are presented in Table 2. None of the nine subjects with an egg SPT wheal size <10 mm failed the baked egg OFC. However, the likelihood of failing the challenge increased with increasing SPT wheal sizes as seen in Fig. 2. Among the subjects who failed the challenge, four subjects had a mild reaction of a rash and/or itchy mouth, three subjects had a moderate reaction with emesis or abdominal pain, and two subjects had a severe reaction (anaphylaxis). One of the anaphylactic subjects was a 9-year-old boy with an egg white-specific IgE of 1.52 kU/L. He did not have a previous SPT to egg. The other case of anaphylaxis was an 8-year-old girl with an egg white-specific IgE of 6.10 kU/L and an egg white SPT wheal of 15 mm. An ovomucoid-specific IgE level was not performed in either subject. Neither of these subjects had a history of anaphylaxis. Both subjects improved after treatment with epinephrine but were hospitalized overnight for monitoring and discharged to home the next morning in good condition.

Figure 3 shows the comparison between egg-allergic children who passed the OFC with those who failed for both egg white SPT and egg white-specific IgE level. There was a trend for a larger SPT wheal diameter in the patients who failed the OFC compared with those who passed, although it did not reach statistical significance (median = 17 mm versus 12 mm; *p* = .091; Fig. 3 A). The negative predictive value for passing the OFC was 100% (nine of nine) if SPT wheal size was <10 mm. ROC curve analysis for SPT wheal size revealed an area under the curve (AUC) of 0.64 (Fig. 4). There was no difference in the egg white-specific IgE levels between patients who failed compared with those who passed (median = 1.52 kU/L versus 2.02 kU/L; *p* = 0.660; Fig. 3 B). ROC curve analysis for egg white-specific IgE revealed an AUC of 0.63 (Fig. 4). Additionally, there was no noticeable difference in ages between the patients who failed when compared with those who passed the OFC (median = 8.8 years versus 7.0 years; *p* = 0.721).

To explore whether the length of time between sensitization testing and food challenge was influential on these findings, a sensitivity analysis was performed limiting the sample to only those who had sensitization testing within 180 days of food challenge. The findings were consistent with that of the primary analysis (data not shown). In fact, there was a statistically significant

Table 2 Characteristics of the children who failed the challenge to baked egg

Sex	Patient 1 Female	Patient 2 Male	Patient 3 Female	Patient 4 Male	Patient 5 Female	Patient 6 Male	Patient 7 Male	Patient 8 Female	Patient 9 Male
Age (yr)	3.1	11.9	9.2	3.5	8.8	9.2	6.2	8.8	5.8
SPT wheal (mm)	25	15	20	10	30	NA	18	15	NA
Ovomucoid IgE (kUA/L)	NA	NA	NA	NA	NA	NA	4.85	NA	NA
Egg white IgE (kUA/L)	NA	0.51	NA	1.04	1.52	1.52	13	6.10	3.89
Challenge outcome	Failed	Failed	Failed	Failed	Failed	Failed	Failed	Failed	Failed
Egg amount ingestion during challenge	1 tbs cake	1 tsp cake	1 tbs cake	1.5 tsp muffin	1 muffin	1 muffin	1/4 muffin	1 muffin	1/2 muffin
Allergic reaction	Mild	Mild	Moderate	Mild	Moderate	Severe	Moderate	Severe	Mild
	Eczema exacerbation	Itchy throat	Emesis, rash on lips, and eczema exacerbation	Erythematous rash	Itchy mouth and abdominal cramps	Anaphylaxis, lip swelling, hives, and vomiting	Throat itching, vomiting, and abdominal pain	Anaphylaxis/hypotension, abdominal pain, and rash	Rash and itching
Treatment of allergic reaction	No	No	Benadryl po	Benadryl po	No	Epinephrine, dexamethasone, and Benadryl	No	Epinephrine, dexamethasone, and Benadryl	No
Outcome after treatment	Good	Good	Good	Good	Good	Good	Good	Good	Good

One teaspoon of muffin or cake contained ~10 mg of egg protein. One tablespoon of muffin or cake contained ~40 mg of egg protein. One-quarter and one-half muffin or cupcake contained ~250 and 500 mg of egg protein, respectively.

SPT = skin-prick test.

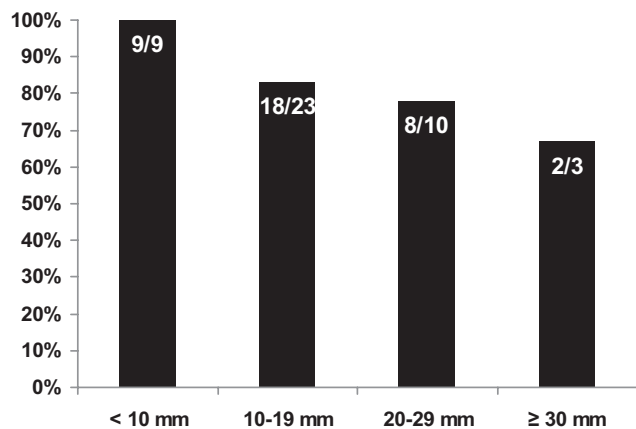


Figure 2. Frequency of passed oral food challenge (OFC) in relation to egg white skin-prick testing (SPT; wheal size in mm).

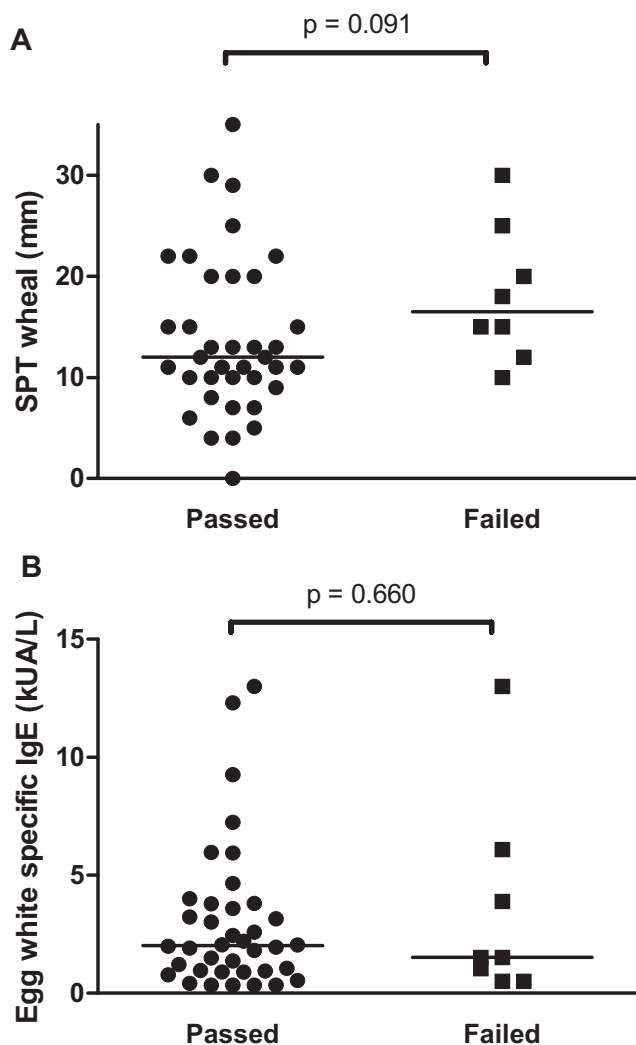


Figure 3. Comparisons between children with egg allergy who passed and those who failed baked egg oral food challenge (OFC) in regard to (A) egg white skin-prick testing (SPT) and (B) egg white-specific IgE.

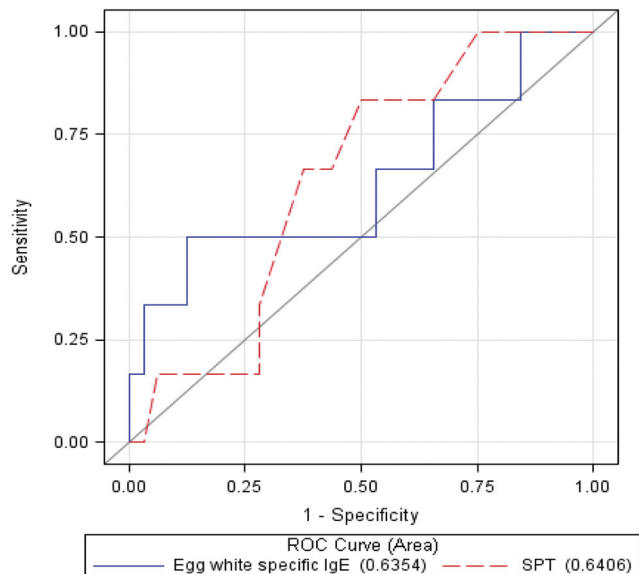


Figure 4. Comparison of receiver operating characteristic (ROC) curves for egg white-specific IgE and skin-prick tests (SPTs) and its area under the curve (AUC). These curves represent the probability of failing an oral food challenge to baked egg at a given value for egg white-specific IgE and SPT ($n = 52$ oral baked egg challenges).

difference in the size of the SPT wheal size between groups (median, SPT failed subjects, 19 mm versus 12 mm, for passed subjects; $p = 0.02$), suggesting that the variability in wheal size may be time sensitive when predicting food challenge failure.

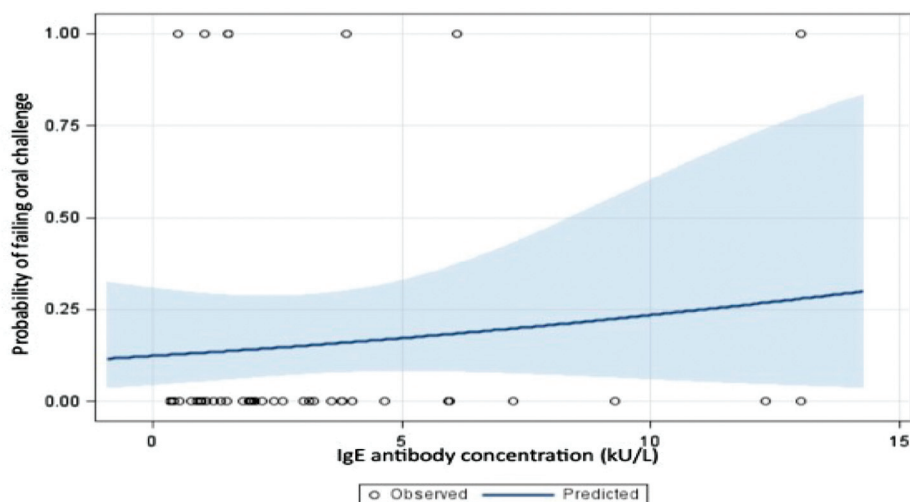
Ovomucoid-specific IgE levels were measured in only seven subjects with a median level of 0.22 kU/L (range, <0.10–4.85 kU/L). Three values were below the LLOD. The subject with the level of 4.85 kU/L failed the challenge, whereas the other six subjects passed the challenge (range, <0.10–1.30 kU/L).

DISCUSSION

In this study, we found that most (83%) of the children with IgE-mediated egg allergy were able to tolerate baked egg by OFC. However, of those who failed, two of nine (22%) had significant anaphylaxis, including hypotension, despite a relatively low egg white-specific IgE level. We were unable to find specific positive predictive cutoff levels for SPT or specific IgE that could predict failing an OFC to baked egg, although SPT appeared more predictive (Fig. 5, A and B). However, an egg white SPT wheal size <10 mm was predictive of passing an OFC 100% of the time. Age of testing was not predictive. Overall, we found that baked egg OFC is safe in most cases.

Cases of anaphylaxis have been reported in previous studies after baked egg OFC. Lemon-Mule *et al.* reported 5 cases required epinephrine among 27 patients who underwent a baked egg OFC.⁵ Konstantinou *et al.*

A.



B.

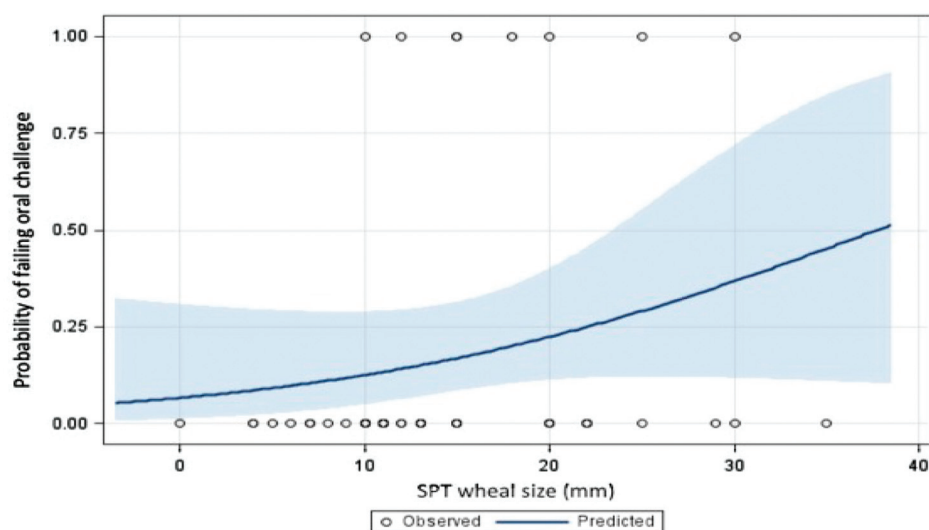


Figure 5. (A) Estimated probability curve for failing oral baked egg challenge at a given egg-specific IgE antibody level derived from logistic regression ($n = 52$ oral baked egg challenges). Outer lines indicate 95% prediction limits. (B) Estimated probability curve for failing oral baked egg challenge at a given skin-prick test (SPT) wheal size derived from logistic regression ($n = 52$ oral baked egg challenges). Outer lines indicate 95% prediction limits. Note that there are multiple overlapping open circles depicted in figures.

found 2 cases of anaphylaxis among 94 patients who underwent a baked egg OFC.⁴ On the other hand, Mankad *et al.* examined the safety of OFC to egg, milk, and peanut in the office setting and found that among 109 patients who underwent the challenge, no one received epinephrine or required hospitalization.¹⁰ These results and ours suggest that although most egg-allergic subjects tolerate baked egg challenges, a small percentage may have anaphylaxis. Furthermore, the two subjects who experienced anaphylaxis did so at the highest dose (one muffin). In Table 2, patients 1–4 all experienced mild to moderate reactions at much lower challenge doses. It could be postulated that if the challenge continued, these individuals would have likely experienced anaphylaxis as well.

Egg white SPT wheal size was the better marker to predict the outcome of the baked egg OFC. All children with an egg white SPT wheal size of <10 mm passed

the challenge, and the rate of passing a challenge declined as the size of the egg SPT wheal increased. To our knowledge, there has not been a published egg white SPT wheal size cutoff below which would predict passing a baked egg challenge in nearly 100% of cases. Lemon-Mule *et al.* reported a $<5\%$ positive predictive value for failing a baked egg challenge with a negative egg white SPT.⁵ However, we did find that a majority of children with even very large egg SPT sizes (>30 mm) were able to tolerate baked egg, suggesting that baked egg challenges even in these patients may not be unreasonable. Egg white-specific IgE level was not a reliable predictive factor in our study. We did not see a difference in egg-specific IgE levels when comparing subjects who passed versus those who failed. Additionally, we identified subjects with very low levels of egg white-specific IgE who failed the challenge; one subject with a level of 1.52 kU/L had anaphylaxis

after the challenge. We did not find the clinical history helpful to predict the success of the OFC. This included history of anaphylaxis, history of severe reaction, other food allergies, family atopic history, and comorbid conditions such as asthma, eczema, or rhinitis. Finally, although the natural history of egg allergy would predict greater success with OFC in older children,^{11,12} we found no significant difference in ages between those who passed and those who failed OFC.

We are limited in that we had a small number of patients who had an ovomucoid-specific IgE level, which has been reported as helpful in predicting the risk of persistent egg allergy or reaction.¹³ Our study did not allow us to analyze the usefulness of this because most clinicians did not routinely obtain ovomucoid-specific IgE levels. However, this marker could be useful when combined with the clinical history, SPT, and egg white-specific IgE.

We chose a standardized baked egg product challenge protocol by using two large eggs baked for at least 30 minutes at a temperature of 375°F. However, we acknowledge that potential variation in baked egg allergen levels does exist, potentially affecting challenge results. We also acknowledge that a standardized extract for the challenges would increase the rigor of this study, but such an extract is not readily available and complicates the feasibility and practicality of conducting such challenges. However, our study does provide practical, real-world implications and evidence that patients who pass these challenges may tolerate products with baked egg that are ubiquitous in various foods, even if they may not tolerate whole egg. It also was conducted in a fashion that other practicing allergists may adapt into their practices. We recognize that passing a baked egg challenge in an observed setting is not definitive evidence of prolonged tolerance to baked egg. Given the retrospective nature of this study, we did not have longitudinal data on patients after passing the baked egg challenge and subsequent intake of baked egg at home. A future, longitudinal prospective study may further our understanding of such patients.

Based on the findings of this study, our suggested baked egg challenge protocol would now include obtaining an egg white SPT, egg white-specific IgE level, and ovomucoid-specific IgE level in every patient being challenged with a more optimal timing between testing and challenge of 6 months. Criteria for making the decision to perform the baked egg challenge would include (1) no anaphylaxis to baked egg within 2 years, (2) SPT wheal size diameter of <35 mm, and (3) ovomucoid-specific IgE of <4 kU/L. Finally, our protocol would incorporate a standard follow-up survey to de-

termine subsequent tolerance to baked egg at home after passing an oral challenge.

In conclusion, we found that most children with egg allergy are able to tolerate baked egg products. However, a physician-monitored challenge is still necessary because we observed two cases of anaphylaxis, despite a relatively low egg-specific IgE level. We found that SPT wheal size was a better marker for OFC outcome to baked egg compared with egg white-specific IgE level. Although our study was unable to identify 90 or 95% positive predictive values for failing baked egg challenges in terms of SPT wheal size and allergen-specific IgE levels, an egg white SPT wheal size of <10 mm was predictive of passing the OFC in 100% of cases. Additional studies should be done to evaluate readily available markers to predict OFC outcomes to baked egg, which could be of clinical benefit to our egg-allergic patients.

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